IN THE UNITED STATES

PATENT AND TRADEMARK OFFICE

APPLICANTS:	Adam T. Zemla
APPLICATION NO.:	10/782,061
FILING DATE:	February 18, 2004
TITLE:	Local-Global Alignment for Finding 3D Similarities in Protein Structures
EXAMINER:	Michael L. Borin
GROUP ART UNIT:	1631
ATTY. DKT. NO.:	IL-11160
F&W REF:	26303-13766US

DECLARATION OF ADAM ZEMLA, PH.D. UNDER 37 C.F.R. § 1.132

Sir:

I, Adam Zemla, Ph.D., hereby declare as follows:

1. I am a Scientist at Lawrence Livermore National Laboratory in Livermore, California in the Computing Applications and Research Group L-174. I received my Master's of Science in Numerical Analysis from Warsaw University in Warsaw, Poland. I completed my doctoral training in Computational Mathematics and Physics at the Moscow University in Moscow, Russia. A true and correct copy of my *Curriculum Vitae* is attached to this declaration as Exhibit A. If called as a witness I could competently testify to the facts and opinions expressed in this declaration.

2. My primary research at Lawrence Livermore National Laboratory relates to protein structure prediction, analysis and modeling. I have served as a principal investigator for projects related to

Protein Classification and Three-Dimensional Protein Structure Prediction in the Pathogen Bio-informatics Group at Lawrence Livermore National Laboratories.

3. For the last twelve years I have developed protein structure prediction algorithms and applied these algorithms to protein structure data for applications ranging from bio-terrorism defense research to drug design. I am the author of several peer-reviewed publications, listed in my *Curriculum Vitae.* Additionally, I have organized the initial Critical Assessment of Techniques for Structure Prediction (CASP) experiments, a community-wide experiment designed to assess the state of the art in protein structure analysis and prediction techniques. I have further published the results from the CASP experiments in peer-reviewed articles.

4. I am an inventor of the claims pending in U.S. patent application 10/782,061 ("the '061 application"). I have reviewed pending U.S. patent application 10/782,061 ("the '061 application"), the office action issued June 11th, 2008 ("Office Action"), and the references cited by the Examiner ("cited prior art").

5. I am familiar with the methods described and claimed for "generating a local-global alignment score which indicates a global and a local similarity between a first protein structure and a second protein structure." *See* instant claim 14. In the claimed method, the local-global alignment score is based on a "longest contiguous segment" and a "global distance test value." The longest contiguous segment is selected based on a plurality of root mean square deviations which are "determined using **a plurality of specified threshold values.**" *Id.*

6. The global distance test value is selected based on a plurality of distance scores which represent a number of residue pairs within "a pre-defined distance of **a plurality of pre-defined distances.**" *Id.*

7. Based on my knowledge and experience, it is my considered opinion that the claimed method for generating a single score, *i.e.*, a "local-global alignment score" based on a longest contiguous segment selected based on a plurality of root mean square deviations which are "determined using a **plurality of specified threshold values**" and global distance test values selected based on a plurality of distance scores which represent a number of pairs of residues within "a pre-defined distance of a **plurality of pre-defined distances**" produces unexpected results as compared to the methods described in the cited prior art, for reasons I explain below.

8. A "local-global alignment score" is a type of protein homology score used to evaluate and generate a protein structure alignment. The majority of protein structure homology algorithms, including those described in the cited prior art, operate by generating a protein structure alignment using a set of internal parameters and then scoring the protein structure alignment. In these protein structure homology algorithms, an alignment of two protein structures is generated and then optimized using an optimization function. Typically, the optimization function is some type of scoring function which evaluates the goodness of the alignment (*e.g.*, a root mean square deviation).

9. In the claimed invention, a "longest contiguous segment" and a "global distance test value" are **selected** based on a "plurality of root mean square values" and a "plurality of distance values," respectively. The "plurality of distance values" and "plurality of root mean square values" are generated using **a plurality of different parameters**, *i.e.*, "**a plurality of specified threshold values**" and "**a plurality of pre-defined distances**":

> A computer-implemented method of generating a local-global alignment score which indicates a global and a local similarity between a first protein structure and a second protein structure, the method comprising:
>
> receiving a protein structure correspondence wherein a plurality of positions in the protein structure correspondence indicates a corresponding pair of residues in the first protein structure and the second protein structure;

determining a **plurality of root mean square deviations** corresponding to a plurality of sets of pairs of residues, wherein each set of pairs of residues comprises a plurality of pairs of residues that are contiguous in the protein structure correspondences and the plurality of root mean square deviations are determined using a **plurality of specified threshold values**;

selecting a longest contiguous segment corresponding to a set of pairs of residues of the plurality of pairs of residues based on the plurality of root mean square deviations;

identifying a **plurality of distance scores**, wherein each distance score corresponds to a number of pairs of residues in the correspondence that are within a pre-defined distance of a **plurality of pre-defined distances**;

selecting a global distance test value based on the plurality of distance scores;

generating the local-global alignment score based on the longest contiguous segment and the global distance test value; and

providing a result based on the local-global alignment score.

Instant claim 14, emphasis supplied.

The generation of the plurality of similarity metrics "root mean square values" and "distance values" using a **plurality of different parameters**, *i.e.,* and **"a plurality** of specified threshold values**"** and "a **plurality** of pre-defined distances**"** allows for the evaluation and selection of a series of intermediate local and global alignments.

10. In my experience, I determined that an optimal threshold value and pre-defined distance could not be selected *a priori* for a set of aligned structures. Consequently, the use of a single threshold value and pre-defined distance can result in a sub-optimal alignment. The instantly claimed invention solves this problem by evaluating intermediate local and global alignments and so allows for the selection of the best local and global alignment from the intermediate local and global alignments by

providing a way to compare results obtained using a number of specified threshold values and pre-defined distances. I explain this in greater detail in the paragraphs below.

11. Generation of intermediate alignments of "superpositions" is described in detail in Zemla et al., "LGA, a method for finding 3D similarities in protein structures", *Nucleic Acids Research,* 2003, Vol. 31, No. 13 ("Zemla *NAR*")[1]:

> An additional problem can arise when structures are similar in small, local regions. These regions of similarity can be overlooked when one global superposition is applied. In general, in many cases there is no 'best' superposition that reveals all regions of similarity between compared proteins. To resolve these problems while comparing two structures, the LGA program generates many different local superpositions to detect regions where proteins are similar.

Zemla *NAR* at page 1, col. 2, lines 12-20.

12. The selection of the best local and global alignment is integral to generating a score that represents the best local and global alignment. Evaluating the intermediate local and global alignments using many different parameters such as "a **plurality** of pre-defined distances" and "a **plurality** of specified threshold values" provides a method of effectively evaluating a large number of alignments while keeping the number of alignments evaluated tractable. The use of multiple distance parameters is discussed in detail in Zemla *NAR*:

> Working with distance analysis (maximum norm) an optimal method for finding the 'best superposition', which will minimize the distances between all selected

[1] The text of Zemla *NAR* is largely incorporated into the priority document of the instant application (*i.e.*, U.S. Provisional Application Serial No. 60/451,292).

> residues, is not known. Results can only be approximated. So to find the 'best' global structural match, GDT uses many distance cutoffs and superpositions.

Zemla *NAR* at page 2, col. 2, lines 12-17.

13. As discussed in paragraphs 10-12, above, evaluating a series of intermediate local and global alignments based on a **plurality of different parameters** provides what I consider to be an unexpected increase in the accuracy of protein structure alignment as compared to the methods of evaluating protein structure alignments described in the cited prior art. This increase in accuracy is tabulated in Table 4 of NAR. A copy of Table 4 is attached as Appendix A to this declaration. The method of instant claim 14 was used to generate the alignments shown in column 7of Table 4, labeled LGA *See, e.g.,* Zemla *NAR* at pg. 3, col. 2, lines 24-30 of NAR.

14. Table 4 lists a set of "difficult" protein structure alignments provided by the claimed LGA method and a set of other commonly-used protein structure alignment programs. For each protein structure alignment generated by each program, Table 4 lists the number of equivalent residues in the alignment and the associated RMSD of the alignment. The "LGA In Comparison With Other Programs" section of the NAR paper describes these unexpected results:

> The number N of structurally equivalent residues differs considerably for several protein pairs. One would expect that a higher number of equivalent residues would indicate better performance of a particular method in the detection of structural similarity. However, comparing the number of equivalent residues is insufficient without taking RMSD into account. RMSD reported by LGA is fairly constant in all cases. Our program can keep the smallest range of RMSD 1.9–2.6 while providing a high number of aligned residues. In a comparison to ProSup, in some cases LGA superimposes more residues under the same distance cutoff (sometimes with a slightly higher value of RMSD).

Zemla *NAR* at pg. 3, col. 2, line 32 – pg. 4, col. 1, line 3.

15. The LGA algorithm thus finds a high number of equivalent residues at a low RMSD value. Although, the other programs listed in the Table may provide a greater number of equivalent residues, they do so at the expense of the RMSD value or vice-versa. For example, line 1 of Table 4 lists the number of equivalent residues and corresponding RMSD values for alignments between the protein structures 1bge-B and 2gmf-A provided by LGA and the other programs. While the DALI and CE other programs provided a larger number of equivalent residues (94 equivalent residues and 107 equivalent residues, respectively) than the LGA program (91equivalent residues), the corresponding RMSD values were much larger (3.3, 3.9 and 2.5, respectively). Similarly, the VAST and ProSup programs provided alignments at slightly smaller RMSD values than LGA (2.3, 2.4 and 2.5 respectively),the number of residues in the alignment produced by the LGA program was much greater (71 equivalent residues, 87 equivalent residues and 91 equivalent residues). The many intermediate local and global alignments generated using the claimed LGA algorithm provides this increase in accuracy.

16. The unexpected results provided by the claimed invention apply with equal force to the methods disclosed in the "Cristobal" reference, "A Study of Quality Measures for Protein Threading Models", cited by the Examiner in the Office Action against claims 17 and 18[2]. Furthermore, it is my opinion that the Cristobal reference teaches away from the claimed invention. I am a co-author of Cristobal and so am intimately familiar with its teachings. Cristobal discusses generating a local and global alignment in very general terms. Cristobal does not teach or suggest the claimed method of selecting a longest contiguous segment from "plurality of pairs of residues" which are "determined

[2] Claim 14, as it is currently amended, incorporates elements similar to those of claims 17 and 18, which are cancelled in the instant response.

using **a plurality of specified threshold values.**" Cristobal further fails to teach or suggest the claimed method of **selecting a global distance test value** from a "plurality of distance scores" which represent a number of residue pairs within "a pre-defined distance of **a plurality of pre-defined distances.**"

17. The portion of Cristobal cited by the Examiner discusses generating a **single** global distance metric "GDT" based on the average of four different measures based on four different distances, "*The measure used in this study was GDT TS, which is the average of four measures with D = 1,2,4 and 8 Å.*"(page 5, col. 1, lines 37-39 of Cristobal).. This average value deterministically produces the same value based on **averaging a** plurality of distance values, not by "**selecting** a global distance test value based on the plurality of distance scores", as required by the claimed invention. Information indicating the best global distance value based on the best metric can be lost or averaged out in the generation of the average value. Accordingly, the cited portion of Cristobal **teaches away** from the claimed method of **selecting a global distance test value** from a "plurality of distance scores" which represent a number of residue pairs within "a pre-defined distance of a plurality of pre-defined distances."

18. In the other portions of the rejection of claims 17 and 18, the Examiner cites sequence-dependent and sequence-independent methods of evaluating protein structure alignment listed in Table 1 of Cristobal and asserts the claimed invention would be obvious given that "it would have been obvious to try the known methods for comparing 3D protein structures, with a reasonable expectation of success." Office Action at pg. 10, third paragraph, lines 8-15. Table 1 of Cristobal includes a listing of different metrics used to evaluate protein structure. Table 1 does not teach or suggest **generating a plurality of a same metric** derived using a **plurality of different parameters,** *i.e.*, "**plurality of root mean square deviations**" and "**a plurality** of **distance scores**" and **selecting**

a "longest continuous segment" or a "global distance test value" based on the plurality of the same metric, as claimed.

19. In my opinion a person of ordinary skill in the art would have understood Table 1 of Cristobal to refer to a list of metrics using defined parameters to evaluate protein structure alignments. Nothing in the table would, in my opinion, lead such a person to the claimed invention which requires the generation of a plurality of values using a same metric and different distance parameters and the selection of the best value. Instead, it is my view that a person of ordinary skill in the art would at best recognize that the different metrics listed in Table 1 can be complimentarily combined to evaluate the quality of protein structure alignment.

12. In conclusion, based on my knowledge and experience, it is my considered opinion that a person having ordinary skill in the art of bio-informatics, working at the time the invention was made, would recognize that the claimed invention produces the unexpected results of generating high quality alignments compared to prior art methods and that there is no teaching or suggestion in the cited art to carry out the method described in claim 14, as amended.

13. I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 12/09/2008 By: _____

APPENDIX A

Table 4. Comparison of structure alignments for 10 'difficult' structures. For each protein pair the N and RMSD results from different methods are provided where N is a number of equivalent residues with the corresponding RMSD

Proteins	VAST	DALI	CE	ProSup	LGA
1bge-B 2gmf-A	71/2.3	94/3.3	107/3.9	87/2.4	91/2.5
1cew-I 1mol-A	75/2.0	81/2.3	81/2.3	76/1.9	79/2.0
1cid 2rhe	78/2.0	96/3.1	97/2.9	84/2.3	93/2.3
1crl 1ede	186/3.7	212/3.6	219/3.8	161/2.6	182/2.6
1fxi-A 1ubq	48/2.1	52/2.5	64/3.8	54/2.6	61/2.6
1ten 3hhr-B	76/1.5	86/1.9	87/1.9	85/1.7	87/1.9
1tie 4fgf	76/1.6	114/3.1	116/2.9	101/2.4	104/2.3
2sim 1nsb-A	299/4.2	289/3.2	275/3.0	248/2.6	269/2.6
2aza-A 1paz	70/2.1	82/3.0	84/2.9	82/2.6	80/2.2
3hla-B 2rhe	58/2.3	74/3.0	83/3.3	71/2.7	74/2.5

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Adam Zemla, Ph.D.

Lawrence Livermore National Laboratory
Computing Applications & Research
Global Security Computing Applications Division, L-174
7000 East Ave., Livermore, CA 94550, USA

Phone: (925) 423-5571
Fax: (925) 423-6437
E-mail: adamz@llnl.gov
Bldg: 132S, Room: 1704

Home address:
986 Country Glen Ln., Brentwood, CA 94513

Phone: (925) 516-4682

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Research Interest

- protein structure analysis and modeling (applications of protein structure analysis/modeling to research efforts in biology)
- mathematical modeling, biological applications
- scientific computing, programming and database development
- numerical analysis, partial differential equations with local singularities

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Professional experience

[09/03-present] Computing Applications & Research (CAR), Global Security Computing Applications Division (GSCAD), LLNL, USA., computer scientist

[2002-03] Computing Applications & Research (CAR), Chemical & Biological National Security Program (CBNP), Biology & Biotechnology Research Program (BBRP), Biodefense Division, Bioinformatics, LLNL, USA., computer scientist

[1999-02] Biology & Biotechnology Research Program (BBRP), Protein Structure Prediction Center at LLNL, USA., biomedical scientist/computer scientist

[1998-99] Applied Science, UC Davis, USA., (Protein Structure Prediction Center at LLNL) research associate

[1996-98] Center of Advanced Research in Biotechnology (CARB), University of Maryland, USA., (Protein Structure Prediction Center at LLNL) research associate

[1994-95] Danish Computer Center for Research and Education, Danish Institute of Mathematical Modelling, UNI*C, Copenhagen, Lyngby, Denmark, computer scientist

[1992-95] BAZA Ltd., Computer company, Warsaw, Poland, manager of UNIX systems dept., also responsible for marketing and trade of UNIX computers

[1992-94] The Mathematical Institute of the Polish Academy of Sciences (IM PAN), Warsaw, Poland, UNIX system administrator

[1987-90] Computational Center of the Mathematical Institute of Soviet Academy of Sciences, Moscow, Russia, mathematician

[1986-99] Numerical Analysis Laboratory of the Mathematical Institute of the Polish Academy of Sciences (IM PAN), Warsaw, Poland, professor associate, researcher

[1981-86] Computational Center of Institute of Nuclear Research (CYFRONET), Swierk, Poland, mathematician, programmer

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Education

M.Sc. Numerical Analysis, Department of Mathematics, Informatics and Mechanics, Warsaw University, Poland

Ph.D. Computational Mathematics and Physics, Department of Computational Mathematics, Moscow University, Russia

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Other professional skills

- Programming languages: C, Fortran, Pascal, PVM, MPI, Java, Perl, HTML
- Operating systems: UNIX, LINUX, Windows

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Involved in projects

- [2006-present] PI on the LLNL LDRD 06-ERD-059 project: A novel structure-driven approach to sequence pattern definition for remote homology detection.
Cooperation with: C. Zhou from LLNL.

- [2004-2005] Co-Investigator on the project: "Plague Plasminogen Activator as a Vaccine Component". The goal of this project is to investigate whether or not the recombinant plasminogen activator of Yersinia pestis can protect against plague infection. Sponsor of the project: Sealy Center for Vaccine Development, University of Texas Medical Branch at Galveston.
Cooperation with: V. Motin from UTMB.

- [2003-2005] PI on the LDRD-ER project: Protein Classification Based on Analysis of Local Sequence-Structure Correspondence.
Cooperation with: T. Slezak and C. Zhou from LLNL.

- [2002-present] Development of a fully automated system for 3D protein structure predictions, development of computational bioinfrastructure at Lawrence Livermore National Laboratory (LLNL).
Cooperation with: T. Slezak (LLNL, USA).

- [2001-present] Application of AS2TS (automated protein structure modeling system) and LGA (protein structure comparison program) to:
a) facilitate the molecular replacement (MR) phasing technique in experimental X-ray crystallographic determination of protein structure.
Collaboration with B. Rupp, B. Segelke from LLNL.
b) modeling proteins in pathogens such as foot and mouth disease virus, west nile virus, and variola virus (smallpox). These models are being used for studies and starting a new effort in designing protein-based pathogen detection signatures.
Collaboration with T. Slezak, P. Fitch, P. McCready and R. Balhorn from LLNL.

- [2001-2003] PI on the LDRD-LW project: Automated 3-D Protein Structure Predictions Based on Sensitive Identification of Sequence Homology (AS2TS).
Cooperation with: T. Slezak and D. Barsky from LLNL.

- [1996-2003] Organizing the CASP process (Critical Assessment of Protein Structure Prediction). Development of a protein structure prediction facility (LLNL & UC Davis & University of Maryland, USA). The project is to establish a

Center for the assessment and development of computational methods of determining protein structure (for more details see http://PredictionCenter.llnl.gov). Structure prediction is a 'grand challenge' problem in high performance computing. The Center is intended to directly support the CASP meetings and to build foundations for the CASP process in general.
Cooperation with: J. Moult (CARB, University of Maryland, USA), T. Hubbard (Sanger Centre, Hinxton, UK), K. Fidelis (LLNL, USA).

- [1994-1995] LAPACK-90. Development of FORTRAN-90 interface for LAPACK (Linear Algebra PACKage), a library of Fortran-77 subroutines for solving the most commonly occurring problems in numerical linear algebra.
Cooperation with: J.J. Dongarra (Oak Ridge Nat. Lab., USA), J.Du Croz & S. Hammarling (Numerical Algorithm Group, Oxford, UK), J. Wasniewski (UNI*C, Denmark).

- [1993-1994] Parallel computing using PVM (Parallel Virtual Machine) and its practical application in image processing when applying methods of wavelets theory.
Cooperation with A. Wakulicz (IM PAN, Poland).

- [1992-1994] Computer Modeling of Stochastic Control Problems. Applying simulated annealing algorithm to search for the solution of an ergodic control cost problem (the results are published in the monograph: W. Runggaldier, L. Stettner "Approximations of discrete time partially observed control problems", Applied Mathematics Monographs, Pisa, 1994).
Cooperation with: L. Stettner (IM PAN, Poland) and W. Runggaldier (Math. Dept. of Padova University, Italy).

- [1990-1992] Computer Modeling of Demografics & Epidemiologics Processes. Applying a nonlinear system of integro - differential equations for modeling demographic and epidemiologic processes. Hypothetical development of the HIV infection in Poland was computed.
Collaboration to Main School of Planning and Statistics, Warsaw, Poland.

- [1987-1990] Difference methods to solve semilinear parabolic equations with nonsmooth initial data.
Cooperation with A. A. Abramov (Computational Center of the Mathematical Institute of Soviet Academy of Sciences, Russia).

- [1985] The Ph.D. thesis "The grid approximation of the diffusion equation with local singularities" (supervisor: A. A. Samarskii and V. B. Andreev, Computational Mathematics, Moscow University, Russia).

- [1981] The M.Sc. thesis "An analysis of some methods of solving parabolic obstacle variational inequalities" (supervisor: M. Dryja, Faculty of Mathematics, Mechanics and Informatics, Warsaw University, Poland).

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Other activities

- member of the organizing committee of CASP (Critical Assessment of Protein Structure Prediction; CASP4 - 2000, CASP5 - 2002)
- member of New York Academy of Sciences
- member of Polish Mathematical Society

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Awards

2002, LLNL 2002 Science and Technology Award for "Rapid Development of Nucleic Acid Diagnostics"

1999, BBRP Achievement Award for CASP project

1994, TEMPUS award for LAPACK-90 project

1982, first prize for the thesis "An analysis of some methods of solving parabolic obstacle variational inequalities" at the competition organized by Polish Mathematical Society

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Selected publications:

S. W. Singer, C. S. Chan, A. Zemla, N. C. VerBerkmoes, M. Hwang, R. L. Hettich, J. F. Banfield, and M. P. Thelen: "Characterization Of Cytochrome 579, An Unusual Cytochrome Isolated From An Iron Oxidizing Microbial Community", Applied and Environmental Microbiology, 2008, v. 74, pp. 4454-4462.

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A. Zemla, C. Ecale Zhou, T. Slezak, T. Kuczmarski, D. Rama, C. Torres, D. Sawicka, D. Barsky: "AS2TS system for protein structure modeling and analysis", Nucleic Acids Research, 2005, 33, pp. W111-W115.

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C. Venclovas, A. Zemla, K. Fidelis, J. Moult: "Assessment of progress over the CASP experiments", PROTEINS: Structure, Function, and Genetics, Vol. 53, Issue S6, 2003, pp. 585-595.

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A. Zemla, C. Venclovas, J. Moult, K. Fidelis: "Processing and evaluation of predictions in CASP4", PROTEINS: Structure, Function, and Genetics, Vol. 45, Issue S5, 2001, pp. 13-21.

C. Venclovas, A. Zemla, K. Fidelis, J. Moult: "Comparison of performance in successive CASP experiments", PROTEINS: Structure, Function, and Genetics, Vol. 45, Issue S5, 2001, pp. 163-170.

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